Utility of the Japan Arteriosclerosis Longitudinal Study Score for Identifying a High Risk for Vasospastic Angina

Akira Funayama, Tetsu Watanabe, Yoichiro Otaki, Satoshi Nishiyama, Takanori Arimoto, Hiroki Takahashi, Tetsuro Shishido, Takuya Miyamoto and Isao Kubota

Abstract

Objective The aim of this study was to investigate whether the Japan Arteriosclerosis Longitudinal Study (JALS) score, which is calculated from the traditional atherosclerotic coronary risk, is associated with the incidence of coronary vasospasms.

Methods We performed vasospasm provocation tests with acetylcholine in 109 patients referred to our hospital due to suspected vasospastic angina and subsequently calculated the atherosclerotic risk score according to the JALS score. Consequently, coronary vasospasms were evoked in 51 patients. The patients were divided into three groups according to the tertile of the JALS score: 1st, <28, n=36; 2nd, 28-41, n=36, 3rd, >42, n= 37. The third tertile exhibited the greatest risk for vasospasms. A multivariate logistic regression analysis revealed that the JALS score (odds ratio: 1.686, p<0.05) was independently associated with the incidence of vasospasms.

Conclusion The JALS score can serve as a useful tool for evaluating patients with suspected coronary vasospasms.

Key words: atherosclerosis, vasospastic angina, JALS score

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Introduction

Coronary vasospasms are associated with the pathogenesis of coronary vasospastic angina (VSA) as well as acute coronary syndrome and various critical cardiac events, such as acute myocardial infarction, sudden cardiac death, serious arrhythmia and syncope (1-3); therefore, risk stratification and the prevention of coronary spasms are crucially important (4). The progression of atherosclerosis is a key determinant of coronary vasospasms (5) and is accelerated by abnormalities in lipid metabolism (6). It has been reported that patients with VSA often exhibit abnormalities in lipid metabolism (7, 8).

The non-high-density lipoprotein cholesterol (HDL-C) level is easily calculated using the total and HDL-C concentrations, the determinations of which are well standardized (9, 10). It has shown the predictive value of non-HDL-C is similar to or better than that of low-density lipoprotein cholesterol (LDL-C) based on the findings of epidemiological studies (11-14). Recently, Tanabe et al. reported that the serum non-HDL-C level is associated with the risk of acute myocardial infarction (AMI) in the Japan Arteriosclerosis Longitudinal Study (JALS) (15). Furthermore, the JALS score, which is calculated from traditional coronary risk factors, including age, blood pressure, diabetes mellitus, smoking and the non-HDL-C level, is a useful tool for assessing an individual’s risk of developing acute myocardial infarction in the Japanese general population (15). Among patients undergoing angiography-based coronary spasm provocation tests with acetylcholine, the frequency of coronary endothelial dysfunction has certainly progressed in recent years. This may be due to a gradual increase in the rates of coronary risk factors, such as dyslipidemia, hypertension and diabetes mellitus (16). Therefore, the JALS score is considered to be effective for predicting the onset of myocardial infarction as well as other cardiovascular diseases. However, the relationship between the JALS score and coronary vaso-
spasms has not been elucidated. The aim of this study was to investigate whether the JALS score predicts the incidence of VSA.

Materials and Methods

Study patients

Angiography-based coronary spasm provocation tests were performed in 149 patients referred to our hospital due to suspected VSA. One hundred and nine patients who exhibited no organic coronary stenosis were enrolled in this study. The exclusion criteria were coronary stenosis (≥50%) (n=34), dilated cardiomyopathy (n=1), severe aortic regurgitation (n=1) and unavailability of laboratory data (n=4). The following coronary risk factors were assessed: hypertension (blood pressure of ≥140/90 mmHg or taking antihypertensive drugs), dyslipidemia (LDL-C level of ≥140 mg/dL or HDL-C level of <40 mg/dL or taking drugs for dyslipidemia), diabetes mellitus (fasting glucose level of ≥126 mg/dL or taking insulin or oral hypoglycemic drugs), body mass index and previous family history of cardiovascular disease. This study used the JALS score, which was developed by Tanabe et al., in addition to a number of risk factors to derive a score from a model predicting the probability of the onset of AMI occurring within the next five years. Specifically, scores were determined based on sex, age, non-HDL-C, HDL-C, blood pressure, diabetes and smoking, with the probability of onset calculated using the total of these scores. The authors created a risk evaluation sheet based on the report by Tanabe et al., which allows for the simple and swift calculation of scores (15). The patients were stratified into three groups according to the JALS score: first tertile= low JALS score (<28), second tertile= medium JALS score (28-41) and third tertile= high JALS score (>42). The study protocol was approved by the institutional ethics committee, and all patients provided their written informed consent.

Induction of coronary spasms

The intracoronary infusion of acetylcholine was performed according to a standard method of provocation testing (17). The administration of vasoactive drugs, including calcium channel blockers, nitrates, beta-adrenergic blockers and other vasodilators, was withdrawn for at least three days before the start of the study. Before performing the vasospasm provocation test with acetylcholine, control coronary arteriography was performed. Acetylcholine was then injected from the same angle into the right coronary artery at a dose of 20 or 50 μg and into the left coronary artery at a dose of 50 or 100 μg each over a period of 20 seconds. Angiography was subsequently performed three minutes from the start of each injection. In the event of ischemic changes on the electrocardiogram (ECG) or chest pain, angiography was performed at that time. Coronary spasms were defined as total or subtotal occlusion (≥90% stenosis) accompanied by episodes of chest pain, ischemic ST-segment changes on the ECG or both. The test was discontinued when coronary spasms were induced.

Laboratory analyses

Blood samples were collected and assessed on admission. General biochemical parameters were measured using routine laboratory methods.

Statistical analysis

The results are presented as the mean ± SD for continuous variables and percentages of the total number of patients for categorical variables. Skewed values are expressed as the median and interquartile range (IQR). Student’s unpaired t-test and the chi-square test were used for comparisons of continuous and categorical variables, respectively. If the data were not normally distributed, the Mann-Whitney U test was used. A logistic regression analysis was performed to evaluate the relationships between the incidence of coronary vasospasms and the parameters. Only the variables that showed significant associations in the univariate analysis were entered into the multivariate analysis. All p values were two-sided, and p values of <0.05 were considered to be significant. The statistical analyses were performed using a standard statistical software package (StatView, version 5.0, SAS Institute Inc, Cary, USA).

Results

Fifty-one patients were diagnosed with VSA based on the provocation of coronary spasms with acetylcholine. The clinical characteristics of the study patients are shown in Table 1. The JALS scores were significantly greater in the patients with VSA than in those without VSA (37.9±12.2 vs. 29.5±13.3, p<0.01). The prevalence of cigarette smoking was significantly higher among the patients with VSA than among those without VSA (51% vs. 24%, p<0.01). The high-sensitivity C-reactive protein (hs-CRP) levels were significantly greater in the patients with VSA than in those without VSA (0.056 mg/dL, IQR 0.031-0.120 vs. 0.030 mg/dL, IQR 0.015-0.083, p<0.01). The use of calcium-channel blockers (CCBs) was significantly more frequent in the patients with VSA than in those without VSA (57% vs. 34%, p<0.01). All patients were classified into three groups according to the JALS score: <28 (n=36, first tertile), 28.3-41 (n=36, second tertile), ≥42 (n=37, third tertile). The incidence of VSA was highest among the patients in the third tertile of the JALS score (Fig. 1). As shown in Fig. 2, the highest third tertile of the JALS score was associated with the highest risk of VSA (3.7-fold compared with the first quartile). In order to assess factors predicting the incidence of VSA, univariate and multivariate logistic regression analyses were performed (Table 2). In the univariate analysis, the JALS score, cigarette smoking and use of CCBs were associated with the onset of VSA. The multivariate analysis revealed that the JALS score was an independent predictor of the incidence of VSA (odds ratio: 1.686, p<
Table 1. Clinical Characteristics of the Study Patients

<table>
<thead>
<tr>
<th></th>
<th>VSA group (n = 51)</th>
<th>Non VSA group (n = 58)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>66.1 ± 10.9</td>
<td>62.0 ± 12.6</td>
<td>0.074</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>33 (65%)</td>
<td>30 (52%)</td>
<td>0.171</td>
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<tr>
<td>BMI, kg/m²</td>
<td>24.2 ± 3.6</td>
<td>23.7 ± 3.9</td>
<td>0.472</td>
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<tr>
<td>Hypertension, n (%)</td>
<td>30 (59%)</td>
<td>31 (53%)</td>
<td>0.573</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>123.1 ± 20.9</td>
<td>127.8 ± 15.8</td>
<td>0.185</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>73.1 ± 12.2</td>
<td>74.4 ± 12.8</td>
<td>0.595</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>4 (8%)</td>
<td>8 (14%)</td>
<td>0.322</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>23 (45%)</td>
<td>19 (33%)</td>
<td>0.187</td>
</tr>
<tr>
<td>Cigarette smoking, n (%)</td>
<td>26 (51%)</td>
<td>14 (24%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Family history of CAD, n (%)</td>
<td>9 (18%)</td>
<td>8 (14%)</td>
<td>0.580</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>5.57 ± 0.66</td>
<td>5.54 ± 0.59</td>
<td>0.817</td>
</tr>
<tr>
<td>TC, mg/dL</td>
<td>185.0 ± 30.7</td>
<td>180.8 ± 33.2</td>
<td>0.496</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>52.2 ± 11.1</td>
<td>59.2 ± 16.6</td>
<td>0.013</td>
</tr>
<tr>
<td>TG, mg/dL</td>
<td>114, 93-164</td>
<td>101, 83-136</td>
<td>0.103</td>
</tr>
<tr>
<td>Non HDL-C, mg/dL</td>
<td>132.7 ± 32.1</td>
<td>120.3 ± 29.6</td>
<td>0.043</td>
</tr>
<tr>
<td>JALS score</td>
<td>37.9 ± 12.2</td>
<td>29.5 ± 13.3</td>
<td>0.001</td>
</tr>
<tr>
<td>hs-CRP, mg/dL</td>
<td>0.056, 0.031-0.120</td>
<td>0.030, 0.015-0.083</td>
<td>0.005</td>
</tr>
<tr>
<td>serum creatinine, mg/dL</td>
<td>0.73 ± 0.18</td>
<td>0.71 ± 0.15</td>
<td>0.401</td>
</tr>
<tr>
<td>BNP, pg/dL</td>
<td>17.5, 9.1-41.5</td>
<td>24.0, 11.9-41.2</td>
<td>0.411</td>
</tr>
<tr>
<td>LVFF, %</td>
<td>70.8 ± 6.7</td>
<td>68.2 ± 11.6</td>
<td>0.206</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Aspirin, n (%)</td>
<td>21 (41%)</td>
<td>17 (29%)</td>
<td>0.195</td>
</tr>
<tr>
<td>Statins, n (%)</td>
<td>11 (22%)</td>
<td>14 (24%)</td>
<td>0.750</td>
</tr>
<tr>
<td>CCBs, n (%)</td>
<td>29 (57%)</td>
<td>20 (34%)</td>
<td>0.019</td>
</tr>
<tr>
<td>ACE-I or ARBs, n (%)</td>
<td>13 (25%)</td>
<td>12 (21%)</td>
<td>0.552</td>
</tr>
<tr>
<td>Betablockers, n (%)</td>
<td>1 (2%)</td>
<td>5 (9%)</td>
<td>0.128</td>
</tr>
</tbody>
</table>


0.05). We additionally performed a multivariate logistic regression analysis including the HDL-C and non-HDL-C levels and excluding the JALS score in order to determine the impact of lipids, including lipoproteins, consequently finding that the non HDL-C level was an independent risk factor for VSA (Table 3).

Discussion

In the present study, the JALS score was found to be effective for predicting the incidence of coronary spasms. One reason why the JALS score can be used to predict the incidence of coronary spasms may be the effects of non-HDL-C. The non-HDL-C level is obtained by subtracting the HDL-C level from the total cholesterol level (11-14). The JALS score is noted to be a new index in the setting of cardiovascular disease, as it represents the level of remnant lipoproteins contained in non-HDL-C and reflects the progression of atherosclerosis (15).

Pharmacological inhibition of the Rho-kinase activity has been demonstrated to protect against atherosclerosis. In a porcine model, the long-term inhibition of Rho-kinase results in the regression of arteriosclerotic coronary lesions (18). Moreover, there is increasing evidence that Rho-
kinase is associated with VSA (19, 20). Rho-kinase inhibitors effectively suppress coronary artery spasms, and the long-term inhibition of Rho-kinase inhibits the development of coronary arteriosclerotic lesions in vivo (21). Interestingly, a close relationship has also been demonstrated between remnant lipoproteins and coronary vasospasms mediated by the upregulation of Rho-kinase (22).

According to the multivariate logistic regression analysis including the HDL-C and non-HDL-C levels, the non-HDL-C level is a risk factor inducing spasms. It is believed that lipoproteins contribute to the onset of spasms in addition to conventional indicators of atherosclerosis (including smoking) and that this phenomenon is reflected in the JALS score. Further studies regarding the impact of lipoproteins on VSA are required in the future.

Elevated levels of oxidative stress and vascular endothelial damage are also associated with the onset of coronary spasms (23, 24). The remnant lipoprotein levels, which are closely related to oxidative stress, are increased in patients with VSA (25, 26). In addition, it has been reported that increased remnant lipoprotein levels are associated with endothelial dysfunction (27). Factors known to provoke endothelial dysfunction include a high age, diabetes mellitus, hypertension and smoking as well as dyslipidemia (28). Smoking, abnormal glucose metabolism and dyslipidemia are also known to be traditional risk factors for VSA (25, 26, 29, 30), and the JALS score is primarily composed of risk factors for vascular endothelial dysfunction. In Japanese patients, abnormal coronary responses to acetylcholine are increased and coronary endothelial dysfunction is progressed. These data indicate that coronary risk factors such as hypertension, dyslipidemia and diabetes mellitus gradually increase in patients with VSA (16). Therefore, a decreased JALS score may be associated with improvements in the coronary endothelial function.

Recently, it has been reported that statins have beneficial effects in suppressing VSA by improving the endothelial function (31). In addition, statins inhibit the pro-atherogenic Rho/ROCK pathway (32), and statin administration may reduce the levels of total cholesterol and low-density lipoprotein-cholesterol, improve endothelial dysfunction and reduce the Rho-kinase activity. Therefore, it is considered to be effective to add a statin in VSA patients with a high JALS score.

In recent years, it has been reported that renal impairment is associated with the onset of VSA (33, 34). However, the JALS score does not act as an index of the renal function. Further studies are needed whether to assess the possible relationship between the renal function and the JALS score.

**Limitations**

In this study, intravascular ultrasound (IVUS), optical coherence tomography (OCT) and other modalities were used during coronary angiography examinations, and it was not possible to observe the areas in which the coronary vasospasms occurred. In future studies, it is necessary to use IVUS and OCT to observe the areas of vasospasms to consider the findings in more detail.

**Conclusion**

An elevated JALS score is significantly associated with
the incidence of coronary spasms. These data indicate that the JALS score can serve as a useful factor for evaluating patients with suspected VSA.

**The authors state that they have no Conflict of Interest (COI).**

**Acknowledgement**

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